REMARKS/ARGUMENTS

A. Overview of claimed invention.

In one broad aspect, the present invention is directed to a process for making a pharmaceutical formulation for oral administration of an active pharmaceutical ingredient comprising applying a solution of the active pharmaceutical ingredient to form a coating on a particulate pharmaceutical substrate, wherein the substrate is free of a polysaccharide.

In another broad aspect, the present invention is directed to a process for making a pharmaceutical formulation for oral administration of an active pharmaceutical ingredient comprising applying a solution of the active pharmaceutical ingredient to form a coating on a particulate calcium pharmaceutical substrate, wherein the substrate is free of a polysaccharide, and the particulate calcium pharmaceutical substrate has been coated with a permeation enhancer.

In even another broad aspect, the present invention is directed to an oral pharmaceutical formulation comprising a particulate pharmaceutical substrate having an application of an active pharmaceutical ingredient coating, wherein the substrate is free of a polysaccharide.

In yet another broad aspect, the present invention is directed to a process for making a pharmaceutical formulation for oral administration of an insulin comprising applying a solution of the insulin to form a coating on a particulate pharmaceutical substrate.

In still another broad aspect, the present invention is directed to a pharmaceutical formulation for oral administration of insulin comprising a particulate pharmaceutical substrate having an application of an insulin coating, wherein the particulate pharmaceutical substrate is free of a polysaccharide.

In certain embodiments, included is a material selected from the group consisting of coating agents, controlled release agents, sustained release agents, pharmaceutical excipient agents, and combinations thereof. In certain other embodiments, the agent is selected from the group consisting of colorants, film-forming polymers, plasticizers, surfactants, permeation enhancers, buffering agents, dispersions of ethyl cellulose, coating lacquers, pigments, and combinations thereof.

B. Misinterpretations of claims by Examiner.

Before discussing the rejections in the Official Action, applicants respectfully point out that throughout the Office Action, the Examiner has made various misinterpretations of the claims, which limitations do not exist. It is respectfully pointed out that the Examiner should have been precise as to exactly which limitations are in which claims, rather than generalizing about limitations being in claims in which those limitations do not appear.

Because of ***Festo***, applicants comment on these misinterpretations as follows, so as to avoid acquiescing in any claim limitations that the Examiner is incorrectly imposing.

(1) Misinterpretations of claims 1, 2, 3, 4, 30, 31, and 55 by Examiner in portion of Office Action vis-à-vis rejection of these claims under 35 U.S.C. Section 102(b) in view of U.S. Patent No. 4,910,021 to Davis et al.

The Examiner stated that claims 1, 2, 3, 4, 30, 31, and 55 are directed to a process for making a pharmaceutical formulation. That is incorrect. Claims 1, 2, 3, 4, 30, and 31 are directed to a process, but claim 55 is a product claim.

The Examiner stated that claims 1, 2, 3, 4, 30, 31, and 55 are directed to the active ingredient being a peptide pharmaceutical. That is incorrect. Claim 2 is directed to the active ingredient being a peptide pharmaceutical, but claims 1, 3, and 4 are directed to any active pharmaceutical ingredient. With regard to claims 30, 31, and 55, they require the active pharmaceutical ingredient to be insulin, which is a type of peptide.

The Examiner stated that claims 1, 2, 3, 4, 30, 31, and 55 are directed to the particulate pharmaceutical substrate being free of a polysaccharide. That is incorrect. Claims 1, 2, 3, and 4 and 55 are directed to the particulate pharmaceutical substrate being free of a polysaccharide, but none of claims 30 or 31 requires the substrate to be free of a polysaccharide.

The Examiner stated that claims 1 and 2 are directed to a capsule coated with a film-forming compound such as ethyl cellulose. That is incorrect. Claims 1 and 2 have no such limitation that the pharmaceutical formulation is a capsule. Also, claims 1 and 2 have no such limitation for a coating of a film-forming compound, whether ethyl cellulose, or any other film-forming coating.

(2) Misinterpretations of claims 1 - 7 and 16 - 22 by Examiner by Examiner in portion of Office Action vis-à-vis rejection of these claims under 35 U.S.C. Section 102(b) in view of U.S. Patent No. 5,811,388 to Friend et al..

The Examiner stated that claims 1 and 16 - 22 are directed to a process for making a pharmaceutical composition. That is incorrect. Claim 1 is directed to a process, but claims 16 - 22 are product claims.

The Examiner stated that claims 1 and 16 - 22 are directed to a layer surrounding the core in which the active pharmaceutical ingredient is concentrated. That is incorrect. Claims 1 and 16 - 22 have no such limitation for a coating layer surrounding the core containing the active pharmaceutical ingredient.

(3) Misinterpretations of claims 1 - 55 by Examiner in portion of Office Action vis-à-vis rejection of these claims under 35 U.S.C. Section 103(a) over U.S. Patent No. 4,910,021 to Davis et al., in view of U.S. Patent No. 5,811,388 to Friend et al., and further in view of U.S. Patent No. 4,596,574 to Urist.

The Examiner stated that claims are directed to a process for making a pharmaceutical formulation. That is incorrect. Claims 1 - 15, 28, 30 - 42, and 54 are directed to a process, but claims 16 - 27, 29, 43 - 53, and 55 are product claims.

The Examiner stated that the claims are directed to the active ingredient being a peptide pharmaceutical. That is incorrect. Claims 2 and 17 are directed to the active pharmaceutical ingredient being a peptide pharmaceutical, but claims 1, 3 - 16, or 18 - 29 are directed to any active pharmaceutical ingredient. Claims 30 - 55 require the pharmaceutical to be insulin, which is a type of peptide.

The Examiner stated that the claims are directed to the particulate pharmaceutical substrate being free of a polysaccharide. That is incorrect. Claims 1 - 29, and 43 - 55 are directed to the particulate pharmaceutical substrate being free of a polysaccharide, but none of claims 30 - 42 requires the substrate to be free of a polysaccharide.

The Examiner stated that the claims are directed to the pharmaceutical formulation being a tablet, the active ingredient being a peptide pharmaceutical, the pharmaceutical ingredients including a controlled release agent or a sustained release agent, the formulation having a coating agent that is a film-forming polymer or a permeation enhancer, and the substrate being calcium

carbonate, calcium citrate, or calcium phosphate. That is incorrect. Not one claim contains all of those limitations. Rather, the limitations appear in various claims. Only four of the claims mention the pharmaceutical formulation being a tablet. These four claims are claims 12, 27, 42, and 53, which are directed to the pharmaceutical formulation encapsulated in a gelatin capsule or compressed into a tablet. Specifically as noted above, only claims 2 and 17 are directed to the active pharmaceutical ingredient being a peptide pharmaceutical. Only nine of the claims mention including a controlled release agent, a sustained release agent, or a coating agent. These nine claims are claims 3, 10, 14, 18, 25, 33, 40, 44, and 51. Furthermore, applicants never stated in any claims that the formulation has a *coating agent* that is a film-forming polymer or a permeation enhancer, but rather, applicants stated that "the agent is selected from the group consisting of colorants, film-forming polymers, plasticizers, surfactants, permeation enhancers, buffering agents, dispersions of ethyl cellulose, coating lacquers, pigments, and combinations thereof" in each of claims 4, 11, 19, 26, 34, 41, 45, and 52. Only four of the claims mention the substrate being calcium carbonate, calcium citrate, or calcium phosphate. These four claims are claims 7, 22, 37, and 48.

The Examiner stated that the claims are further directed to the pharmaceutical formulation formed by the process having the active agent compressed on particulate calcium phosphate and having a coating agent selected from ethyl cellulose, permeation enhancer, or surfactant. Applicants never stated in any claims that the pharmaceutical formulation has the active agent compressed on particulate calcium phosphate. Rather, applicants stated that the active pharmaceutical agent forms a *coating* on a particulate pharmaceutical substrate, and sometimes the substrate is particulate calcium phosphate, and sometimes the substrate with coating of active pharmaceutical agent is compressed into a tablet. Furthermore, applicants never stated in any claims that the formulation has a *coating agent* selected from ethyl cellulose, permeation enhancer, or surfactant, but rather, applicants stated that "the agent is selected from the group consisting of colorants, film-forming polymers, plasticizers, surfactants, permeation enhancers, buffering agents, dispersions of ethyl cellulose, coating lacquers, pigments, and combinations thereof" in each of claims 4, 11, 19, 26, 34, 41, 45, and 52.

C. Discussion of Rejection of claims 1, 2, 3, 4, 30, 31, and 55, as being anticipated under 35 U.S.C. Section 102(b) by U.S. Patent No. 4,910,021 to Davis et al.

As the Examiner should be well aware, for a reference to be a reference under 35 U.S.C. Section 102(b), that reference, by itself, much teach each and every element of the claim. That is not achieved by Davis et al.

More specifically, Davis et al. do not teach, nor suggest, particulate pharmaceutical substrates, and thus, do not teach, nor suggest, applying an insulin solution, nor any other pharmaceutical solution, as a coating on a particulate pharmaceutical substrate. Davis et al. are silent vis-à-vis particulate substrates, let alone a calcium material as a particulate substrate to be coated. Rather, they mention insulin and various other peptide pharmaceuticals in a formulation for oral administration, and specifically, they teach mixing sodium lauryl sulfate, cetyl alcohol, and a solution of insulin, as the peptide pharmaceutical, with heating at 40 °C. The heating at 40 °C dissolves the sodium lauryl sulfate and the cetyl alcohol in the insulin solution, forming an oily dispersion. That oily dispersion is placed inside a gelatin capsule. The coating in Davis et al., which is an aromatic acid coating, is an enteric coating on the outside of a gelatin capsule. See, column 7 of Davis et al.

Independent claim 1, and thus, each dependent claims 2, 3, and 4 (which depend back to independent claim 1 and hence incorporate the limitations of claim 1 by reference), and also independent claim 30, and thus, dependent claim 31 (which depends back to independent claim 30 and hence incorporates the limitations of claim 30 by reference), require "applying a solution of the active pharmaceutical ingredient to form a coating on a particulate pharmaceutical substrate".

As noted, Davis et al. do not teach, nor suggest, particulate pharmaceutical substrates, and thus, do not teach, nor suggest, applying an insulin solution, nor any other pharmaceutical solution, as a coating on a particulate pharmaceutical substrate. Thus, Davis et al. do not anticipate any of claims 1, 2, 3, 4, 30, or 31 under 35 U.S.C. Section 102(b), and the Examiner is respectfully requested to withdraw the rejection.

Independent claim 55 requires an oral pharmaceutical formulation of "a particulate dibasic calcium phosphate dehydrate pharmaceutical substrate having an application of an insulin coating", where the insulin is in certain amounts.

As noted, Davis et al. do not teach, nor suggest, particulate substrates, and specifically, they do not mention a calcium material as a particulate substrate having a coating of insulin. Davis et al. are absolutely silent with regard to calcium. Thus, Davis et al. do not anticipate

claim 55 under 35 U.S.C. Section 102(b), and the Examiner is respectfully requested to withdraw the rejection.

D. Discussion of Rejection of claims 1 - 7, 14, and 16 - 22, as being anticipated under 35 U.S.C. Section 102(b) by U.S. Patent No. 5,811,388 to Friend et al.

As the Examiner should be well aware, for a reference to be a reference under 35 U.S.C. Section 102(b), that reference, by itself, much teach each and every element of the claim. That is not achieved by Friend et al.

More specifically, Friend et al. mention insulin and other peptide pharmaceuticals in a formulation for oral administration. The focus of Friend et al. is on the formulation having an excipient that is free of any enteric polymeric material or gas-forming material. Contrary to the Examiner's allegations that Friend et al. in column 12 list various materials, such as EMCOMPRESS (calcium phosphate), as the carrier or substrate that is coated by the pharmaceutical, rather Friend et al. disclose in column 12 that these materials are used as excipients, and do not disclose that these materials are used as the carrier or substrate that is coated by the pharmaceutical. In connection with this, the Examiner also has ignored that at column 16, lines 44 - 45, Friend et al. teach that "Suitable carriers include such material as sugars (i.e., lactose)...." This means that Friend et al. specifically teach a substrate (what is coated by the pharmaceutical) that has a polysaccharide, and thus, Friend et al. do not teach a substrate free of a polysaccharide.

Thus, Friend et al. contain a teaching away from the claimed invention as all of claims 1 - 7, 14, and 16 - 22 require that the particulate substrate "is free of a polysaccharide".

Since Friend et al. do not teach, nor suggest, a particulate substrate free of a polysaccharide, but rather specifically teach that suitable carriers include such material as sugars (i.e., lactose), which is a teaching away from the claimed invention, then, Friend et al. do not anticipate any of claims 1 - 7, 14, or 16 - 22 under 35 U.S.C. Section 102(b), and the Examiner is respectfully requested to withdraw the rejection.

Also, claims 6, 7, 14 and 22 require that the substrate is a calcium material. As noted, Friend et al. teach calcium phosphate as an excipient, not as a substrate, and instead teach that the substrate is sugars. Thus, for this additional reason, Friend et al. do not anticipate any of

claims 1 - 7 or 16 - 22 under 35 U.S.C. Section 102(b), and the Examiner is respectfully requested to withdraw the rejection.

E. Rejection of claims 1 - 55, as being obvious under 35 U.S.C. Section 103(a) over U.S. Patent No. 4,910,021 to Davis et al., in view of U.S. Patent No. 5,811,388 to Friend et al., and further in view of U.S. Patent No. 4,596,574 to Urist.

Applicants' comments above, with regard to Davis et al. and Friend et al., are reincorporated here by reference.

Further with regard to Friend et al., applicants respectfully point out that the Examiner has ignored that Friend et al. have no actual example with insulin, but simply mention insulin in a large list of various peptide pharmaceuticals, and thus, Friend et al. fail to appreciate the problem with an orally swallowed formulation of insulin.

With regard to Urist, applicants respectfully point out that Urist discloses an implant that is a drug delivery system for delivering the drug bone morphogenic protein (BMP) from a ceramic matrix. The ceramic matrix may be tricalcium phosphate.

However, applicants respectfully submit that the Examiner is misinterpreting Urist. Although the Examiner is correct that the implant may be in oral tissue, that does not mean the implant causes oral administration of the BMP pharmaceutical, but rather means the implant causes administration by absorption through the mucous membranes of the oral tissue, for instance, buccal administration or sublingual administration of the BMP pharmaceutical. Oral administration, to which applicants' claims are limited, means the pharmaceutical is swallowed. An implanted matrix that is a drug delivery system is not swallowed.

Accordingly, Urist is non-analogous art. The *Graham v. John Deere* court case that the Examiner cites on page 4 of the Office Action for a list of what constitutes obviousness is an old case from 1966. As the Examiner should be aware, there are court cases on obviousness that are much more recent. The Examiner is referred to *Hodosh v. Block Drug*, 786 F.2d 1136 (Fed. Cir. 1986), which clearly states that any prior art must be considered as a whole and compared to the claimed invention as a whole. The Examiner is not considering Urist as a whole. The Examiner is not considering the present claims as a whole. Picking and choosing from a reference, while ignoring the rest of the reference is impermissible.

Contrary to the Examiner's allegations, the following is what is taught to the person of ordinary skill in the art from combining Davis et al., Friend et al., and Urist.

The focus in Davis et al. is on the coating over a gelatin capsule that contains an oily dispersion of a pharmaceutical, such as insulin, the capsule being for oral administration. Davis et al. have nothing about particulate substrates, and thus nothing about a coating of a pharmaceutical on a particulate substrate, such as a calcium material. The focus of Friend et al. is on a peptide pharmaceutical formulation for oral administration having an excipient that is free of any enteric polymeric material or gas-forming material. Friend et al. have no actual reduction to practice with insulin as the peptide, and thus fail to appreciate the problems of orally administered insulin, let alone the desire to have an oral insulin formulation that is free of a polysaccharide. That is why Friend et al. specifically teach sugar, which is a polysaccharide, as the substrate or carrier to be coated with various peptide pharmaceuticals for oral administration. Friend et al. do not teach calcium phosphate as the substrate, but rather teach calcium phosphate as an excipient. Urist teaches a ceramic matrix which may be tricalcium phosphate and which contains BMP. The BMP-containing matrix is implanted, and thus, cannot be swallowed, even if implanted in oral tissue. Rather, if the implant is in oral tissue, the BMP is absorbed through the mucous membranes of the oral tissue. Urist has nothing about pharmaceutical formulations for oral administration.

Thus, Davis et al., Friend et al., and Urist, either alone, or in any combination whatsoever, do not render obvious any of claims 1 - 55 under 35 U.S.C. Section 103(a), and the Examiner is respectfully requested to withdraw the rejection.

CONCLUSIONS

Applicants respectfully submit that none of claims 1, 2, 3, 4, 30, 31, and 55 is anticipated under Section 102(b) in view of U.S. Patent No. 4,910,021 to Davis et al., and applicants respectfully submit that none of claims 1 - 7, 14, and 16 - 22 is anticipated under Section 102(b) in view of U.S. Patent No. 5,811,388 to Friend et al. Also, applicants respectfully submit that none of claims 1 - 55 is obvious under Section 103(a) over U.S. Patent No. 4,910,021 to Davis et al., in view of U.S. Patent No. 5,811,388 to Friend et al., and further in view of U.S. Patent No. 4,596,574 to Urist.

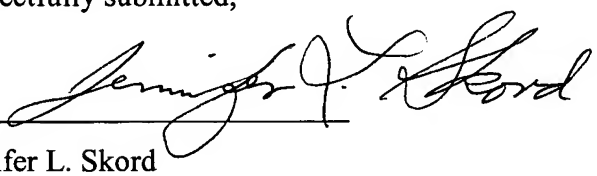
Accordingly, applicants respectfully request the Examiner to withdraw all of the rejections, and respectfully submit that the application is in condition for allowance. Early allowance is earnestly solicited.

DEPOSIT ACCOUNT

Although it is believed that no fee is due, the Commissioner is authorized to charge any deficiencies of payment associated with this communication, or to credit any overpayment, to **Deposit Account No. 13-4365.**

Respectfully submitted,

Date: October 19, 2004

By: 

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